REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-3 and 7-10 are in this case. Claims 1, 2 and 7-10 have been withdrawn from consideration and are now also canceled. Claim 3 has been rejected. No Claims have been allowed. Claim 3 has now been amended.

35 U.S.C. §112, First Paragraph, Rejections

The Examiner has rejected claim 3 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to make and/or use the invention. The Examiners rejections are respectfully traversed. Claim 3 has now been amended.

The Examiner has stated that while the specification clearly discloses no detectable expression of the hpa gene in peripheral white blood cells from CLL and NHL patients, and positive expression in cells from all of the AML and ALL patients, one of ordinary skill would be unable to distinguish whether a patient had CLL or NHL solely based on the claimed method of detecting expression of hpa in peripheral white blood cells, without consideration of additional factors, such as the methods of diagnosing AML, ALL, CML and NHL taught in the Merck Manual. Further, the Examiner has stated that a discrepancy was noted between different methods of detecting heparanase gene expression (i.e. RT-PCR and catalytic activity with HSPG substrate) in white blood cells. Yet further, the Examiner has indicated the possible existence of other human heparanases distinct form the human heparanase encoded by a polynucleotide as set forth in SEQ ID NO: 1.

The present invention is of heparanase specific molecular probes which can be used detection and monitoring of malignancies, metastases, and non-malignant conditions, specifically as a novel method of distinguishing between different types of hematopoietic tumors based on the surprising results disclosed in the instant specification (Table 1, page 57, and Figures 13, 14 and 15) Applicant is of the strong opinion that detection of human heparanase expression provides a novel means with which to make a clinically accurate distinction, in individuals suspected of having blood cancer, between patients having differentiated B cell lymphoma such as CLL and NHL, and those having undifferentiated myelocytic and lymphoblastoid

leukemia such as ALL and AML. That notwithstanding, to further clarify and define the scope of the present invention, and to expedite prosecution in this case, as recommended by the Examiner during the abovementioned telephone interview of October 30, 2003, currently amended claim 3 now recites:

> "A method of detecting expression of a human heparanase gene which comprises a polynucleotide sequence as set forth in SEQ ID NO:1 in a human individual suspected of suffering from a blood cancer, the method comprising monitoring an RNA expression of said human heparanase gene in white blood cells of said individual."

Thus, currently amended claim 3 now reads on detection of RNA expression of human heparanase encoded by SEQ ID NO: 1. Applicant wishes to point out that the polynucleotide of SEQ ID NO:1 has been disclosed in U.S. Patent No. 5,968,822, to Pecker et al, issued October 19, 1999 (see SEQ ID NO:9), of which the instant application claims priority.

Further, currently amended claim 3 now reads on detecting human heparanase gene expression by monitoring heparanase RNA. Such detection, using heparanse-specific molecular probes and well-known methods such as RT-PCR, in-situ hybridization and Northern blotting, is described throughout the instant specification, for example, on page 48, line 15, to page 49, line 17:

> "***Expression of the heparanase gene in various cell types and tissues (RT-PCR):***
>
> RT-PCR was applied to evaluate the expression of the *hpa* gene by various cell types. For this purpose, total RNA was reverse transcribed and amplified, using the following cDNA primers: Human *hpa* - Hpu-355 5'-TTCGATCCCAAGAAGGAATCAAC-3' (SEQ ID NO:6) and Hpl-229 - 5'-GTAGTGATGCCATGTAACTGAATC-3' (SEQ ID NO:7).
>
> ***Expression pattern of the heparanase gene transcript (in situ hybridization).***
>
> *In situ* hybridization enables determination of the distribution of *hpa* transcripts in normal and malignant tissues. For this purpose, thin sections of biopsy specimens were processed for *in situ* hybridization and hybridized with an antisense RNA probe to the *hpa* gene. The experiments have the resolution power to unambiguously identify the expressing cell type, be they tumor cells, tissue macrophages, mast cells or platelets. Sections were treated with proteinase

> K to expose the target RNA and to block non specific binding sites before addition of the probe (34). For *in situ* hybridization, two digoxigenin labeled probes were prepared, one in the sense direction and the other in the anti-sense direction. They were both transcribed from a fragment of about 624 bp of the *hpa* cDNA sequence (nucleotides 728-1351, SEQ ID NOs: 1 and 3) cloned in to the *Eco*RI-*Hind*III sites of the transcription vector pT3T7-Pac (a modified vector derived from pT3T7, Pharmacia), using T3 (for antisense) or T7 (for sense) RNA polymerase, according to the suppliers protocol. Slides were hybridized under appropriate conditions with the labeled probe and the hybridized probe is visualized using colorimetric reagents (NBT & BCIP) (34). Reactions were stopped when the desired intensity has been reached."

Thus, the instant specification provides one of ordinary skill in the art with generous guidance as to how to practice the method of the instant invention as disclosed in currently amended claim 3.

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph rejections.

In view of the above amendments and remarks it is respectfully submitted that claim 3 is now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

An early and favorable action is therefore respectfully requested.

Respectfully submitted,

Sol Sheinbein
Registration No. 25,457

Date: October 30, 2003